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09/920,000	07/31/2001	Peter H. Kay	9236/2002	7078

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PALMER & DODGE, LLP
PAULA CAMPBELL EVANS
111 HUNTINGTON AVENUE
BOSTON, MA 02199

EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/920,000	Applicant(s) KAY, PETER H.	
	Examiner Jeanine A Goldberg	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/8/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

1. This application claims priority to PCT/AU00/00053, filed February 2000 and Australian foreign application PP8448, filed February 1999.

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Australia on February 1, 1999. It is noted, however, that applicant has not filed a certified copy of the Australian application as required by 35 U.S.C. 119(b).

Drawings

2. The drawings are approved by the examiner.

Claim Objections

3. Claims 1, 9, 11 are objected to because the claim does not end in a period (see MPEP 608.01(m)). This objection may be overcome by inserting a period at the conclusion of Claim 1, 9, 11.

Sequence Rules

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

Claims 9, and 11 contain sequences which are not identified by SEQ ID NO. Based upon the specification, it appears as though each of the sequences should be labeled SEQ ID NO: 1-5 respectively.

Information Disclosure Statement

5. The listing of references in the specification, page 21, is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-19 are indefinite because Claim 1 does not contain a final process step which relates back to the preamble. The preamble states that the method is for detecting methylated nucleic acids but the final process step is measuring the change in fluorescence. Therefore the claims are unclear as to whether the method is a method of detecting methylated nucleic acids or measuring change in fluorescence. A final

process step which clearly relates back to the preamble may be "wherein a decrease in fluorescence indicates unmethylated nucleic acids".

B) Claims 3-6 are indefinite over the recitation "at least about" because the metes and bounds of the invention are not clear. As the CAFC noted, and affirmed, regarding the district court determination of this phrase in Amgen Inc. v. Chugai Pharmaceutical Co. Ltd. (CA FC) 18 USPQ2d 1016 at page 1031 "the court held the "at least about" claims to be invalid for indefiniteness." Here too, the situation is that there is close prior art, applied as a 102(b) for a lower limit value, and the claim is indefinite with regard to the values encompassed. The claims may be amended to either chose "at least" or "about" where there is a definite lower limit or "about" where there is no definite lower limit. Claim 4 recites "at least about up to 35". This phrase is indefinite as to the range it encompasses. "At least means" greater than 35, "about" means around 35 and "up to" means less than 35. Therefore, there is no clear meaning to the phrase "at least about up to 35 nucleotides".

C) Claims 9, 11 are indefinite because the claims do not properly refer to the sequences in the alternative. It appears as though they claims may be directed to a Markush type group which requires, commas between the alternatives and an "and" prior to the final alternative. The instant claims do not contain any conjunction between the elements. Appropriate correction is requested. Moreover, the claims recite "the labeled oligonucleotide sequence", however, this recitation lacks proper antecedent basis. The claims from which Claim 9 depend do not recite a specific "labeled

oligonucleotide sequence". The claims define a labeled stem sequence and a loop sequence, but not a "labeled oligonucleotide sequence.

D) Claim 19 is indefinite because it is unclear what a "method according to claim 1 substantially as describe herein before described" encompasses. The term "substantially" in claim 19 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Moreover, it is unclear what degree of substantially is required. It is unclear whether the method would merely require FRET or whether the method requires methylation. It appears as though applicants are trying to claim the doctrine of equivalents. The doctrine of equivalents does not normally arise but in the context of an infringement action, wherein the court deems what the "equivalents" encompass. Therefore, a claim directed to the doctrine of equivalents is not definite and clear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application

> by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

7. Claim 18 is rejected under 35 U.S.C. 102(e) as being anticipated by Tyagi et al (US Pat. 6,037,130, March 2000).

It is noted that the kit claim is directed to a product claim which comprises a labeled oligonucleotide sequence. The intended use of the product for distinguishing methylated and non-methylated nucleic acids as used in Claim 1 do not impart any strucutural limitations on the claims which are not taught by the reference.

Tyagi et al. (herein referred to as Tyagi) teaches a kit comprising a detector probe which is a fluorescently labeled hairpin forming oligonucleotides containing a fluorescent emitter and a quencher(limitations of Claim 18)(col. 25, Claim 18).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-6, 14-17, 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elsas, II et al. (US Pat. 6,207,387, March 27, 2001) in view of either Ehrlich et al. (Biochimica et Biophysica Acta, Vol. 395, pages 109-119, 1975) or Hua et al. (Gov. Rep. Announce. Index US, Vol. 88, No. 18, Abstract No. 847,050 1988) and in further view of either Tyagi et al (US Pat. 6,150,097, November 2000) or Coull et al (US Pat. 6,355,421, March 2002).

Elsas, II et al. (US Pat. 6,207,387, March 27, 2001) teaches detecting mutations in genes by determining the melting temperature of the hybrid of the amplified DNA and the specific oligonucleotide (col. 10, lines 20-25). Elsas teaches that "under identical conditions, two strands that are not exactly complementary, differing by even one nucleotide, will be less stable and will dissociate at a temperature which exactly complementary hybrids remain paired (col. 8, lines 50-57). Elsas teaches that the melting temperature between a mismatched hybrid will denature at a lower temperature than a exact matched hybrid (col. 10, lines 37-40). Elsas also teaches that fluorescence energy transfer is a specific application of this approach (col. 10, lines 49-50). Elsas teaches the different melting temperatures for the allele specific probe and detection of fluorescence (col. 11).

While Elsas teaches detecting different nucleic acids based upon melting temperature, Elsas does not specifically teach the structure of fluorescence energy transfer and does not teach using the fluorescence energy transfer for detecting methylation.

Erlich teaches Xanthomonas phage XP-12 DNA containing 5-methylcytosine completely replacing cytosine, has the highest reported melting temperature for any naturally occurring DNA (abstract). The melting temperature is 6.1 degrees Celsius higher than normal DNA containing the same percentage of adenine plus thymine (abstract), page 114). As seen in Figure2, the XP-12 DNA has a higher melting temperature (page 114).

Similarly, Hua teaches that the melting temperature of methylated Z-DNA is 387K which is 7K higher than a similar calculation for unmethylated B-DNA which is in agreement with observation (abstract).

Moreover, Tyagi et al. (herein referred to as Tyagi) teaches using nucleic acid hybridization probes having a first conformation when not interacting with a target and a second conformation when interacting with a target and having the ability to bring a label pair into touching contact in one formation but not the other (abstract). Tyagi teaches using quenching molecules and other fluorophores as efficient quenching moieties for fluorophores when attached to nucleic acid hybridization probes (col 3, lines 40-43)(limitations of Claim 2). The probes of Tyagi contain a hairpin structure which comprise single stranded loop of the hairpin and two arm sequences which form a double stranded stem hybrid (col. 5, lines 10-15). Tyagi teaches that the molecular beacon probes may have target recognition sequences 7-140 nucleotides in length (col 5, lines 24-25)(limitations of Claims 3-6). Additionally Tyagi teaches the arms that form a stem hybrid or stem duplex are 3-25 nucleotides in length (col. 5, lines 26-

27)(limitations of Claim 16). Tyagi teaches a kit which contains a hairpin probe with labels (col 19, lines 66-67, Claim 12)(limitations of Claim 18).

Coull et al. (herein referred to as Coull) teaches methods of detecting target sequences using a probe which has a measurable change in one property of at least one donor or acceptor moiety of the probe which can be used to detect, identify or quantitated the target sequence in a sample. As seen in Figure 11, configuration III, a probing segment is flanked on either side by a arm segment and either a quencher and fluorophore. The hairpin loop and stem structure allows energy transfer between donor and acceptor moieties linked at opposite ends of the nucleic acid polymer (col. 7, lines 30-37). The probing segments is designed to hybridized to at least a portion of a target sequence (col. 8, lines 35-36). In the method of Coull, a sample is contacted with the molecular beacon and a change in detectable signal associated with at least one donor or acceptor moiety of the probe is detected, identified or quantitated. Coull teaches that the assay may be used to detect a target sequence which is specific for a genetically based disease including cancer. Coull teaches that the probing sequence hybridizes to the entire target sequence (col. 16, lines 20-25). The probing sequence will generally have a length between 5-30 units in length (col. 16, lines 32-34)(limitations of Claims 3-6). The arm segments are 2-6 units in length (limitations of Claim 16). Coull teaches that shorter probes are less costly to synthesize, are generally easier to purify and should exhibit few non-specific interactions since they will comprise less nucleobase sequence diversity (col. 20, lines 29-32)(limitations of Claim 15). Coull teaches kits which comprise one or more PNA Molecular Beacons (col. 24, lines 51-67)(limitations of

Claim 18). Coull teaches considerable analysis of the Tm melting temperature for the stem-loop hairpin probes (col. 20, 37-44). Coull teaches that the probes exhibit a low inherent noise (background) and an increase in detectable signal upon binding of the probe to a target sequence (col. 7, lines 40-42).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the method of Elsas for detecting different nucleic acids based upon different hybridization properties including melting temperatures with the teachings of either Tyagi or Coull which discuss and describe stem-loop and fluorescence energy transfer with the teachings of either Ehrlich or Hua teaching the properties of methylated DNA. Detecting nucleic acids based upon different melting temperatures and dissociation properties was used to identify mismatches in nucleic acids. Both Ehrlich and Hua teach that methylated DNA and unmethylated DNA have different melting temperatures. The ordinary artisan would have recognized based upon the teachings that in the art, namely Ehrlich and Hua, that in addition to mismatched DNA, methylation could also be detected based upon different melting temperature and dissociation rates. Combining the teachings of Elsas and either Ehrlich or Hua would yield an assay which would detect methylated nucleic acids as compared to unmethylated nucleic acids. Detection of methylated nucleic acids as compared to unmethylated nucleic acids is of interest to the clinical diagnostics because numerous genes are methylated in cancer as compared to unmethylated in normal tissue. Therefore, combining the teachings of Elsas and Ehrlich or Hua, a hybridization assay for differentiation methylated DNA from unmethylated DNA does not require the use of enzymes, solid supports would facilitate

the detection of methylation in genes and may be used as an indicator for cancer. Moreover, the use of hairpin stem-loop probes with fluorophores and quenchers for detecting target nucleic acids in samples is taught by both Tyagi and Coull would have provided a fluorescent detection assay which is easily detectable in a single tube which does not require subjection to a gel or solid support. The use of FRET allows for the direct detection of nucleic acid target sequences without the requirement that labeled nucleic acid hybridization probes or primers be separated from the hybridization complex prior to detection (Coull et al. col. 1, lines 45-50). Therefore, using the specific teachings about fluorescence energy transfer techniques, as described in Coull and Tyagi, would facilitate the fluorescence energy transfer method for detecting different nucleic acids as taught by Elsas. Therefore, given all of the teachings well known in the art, at the time the invention was made, a FRET-like method for detection of different nucleic acids based upon the know property that methylated and unmethylated DNA molecules have different hybridization properties would have been obvious to the ordinary artisan.

9. Claims 7, 10, 12, 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elsas, II et al. (US Pat. 6,207,387, March 27, 2001) in view of either Ehrlich et al. (Biochimica et Biophysica Acta, Vol. 395, pages 109-119, 1975) or Hua et al. (Gov. Rep. Announce. Index US, Vol. 88, No. 18, Abstract No. 847,050 1988) and in further view of either Tyagi et al (US Pat. 6,150,097, November 2000) or Coull et al (US Pat.

6,355,421, March 2002) as applied to Claims 1-6, 14-19 above, and further in view of Herman et al. (US Pat. 6,265,171, July 2001).

The combination of Elsas, Ehrlich or Hua and Tyagi or Coull does not specifically teach detecting methylation in GSTpi or calcitonin which is differentially expressed in cancer versus a normal state.

However, Herman et al. (herein referred to as Herman) teaches numerous genes which are differentially methylated at CpG islands in neoplastic versus normal tissue (limitations of Claim 7). These genes include GSTpi and calcitonin (limitations of Claims 10, 12). Herman also teaches that CpG island differential methylation may be detected in prostate cancer (col. 112, Claim 12)(limitations of Claim 12). Aberrant methylation in the 5' promoter of E-cadherin is prostate, breast and many other carcinomas (col. 27, lines 5-10).

Therefore, using the method of Elsas, Ehrlich or Hua and Tyagi or Coull in view of the teachings of differential methylation in gluthathione-S-transferase-II(pi) and calcitonin. The ordinary artisan would have been motivated to have detected methylation in these two specific genes because Herman teaches that they contain methylated CpG neoplastic versus normal tissue.

10. Claims 7, 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elsas, II et al. (US Pat. 6,207,387, March 27, 2001) in view of either Ehrlich et al. (Biochimica et Biophysica Acta, Vol. 395, pages 109-119, 1975) or Hua et al. (Gov. Rep. Announce. Index US, Vol. 88, No. 18, Abstract No. 847,050 1988) and in further

view of either Tyagi et al (US Pat. 6,150,097, November 2000) or Coull et al (US Pat. 6,355,421, March 2002) as applied to Claims 1-6, 14-19 above, and further in view of Kay et al (Leukemia and Lymphoma, Vol. 24, pages 211-220, 1997).

The combination of Elsas, Ehrlich or Hua and Tyagi or Coull does not specifically teach detecting methylation in Myf-3 which is differentially expressed in cancer versus a normal state.

However, Kay et al. (herein referred to as Kay) teaches the Myf-3 gene is abnormally hypermethylated in non-Hodgkins lymphoma (abstract).

Therefore, using the method of Elsas, Ehrlich or Hua and Tyagi or Coull in view of the teachings of differential methylation in gluthathione-S-transferase-II(pi) and calcitonin. The ordinary artisan would have been motivated to have detected methylation in these two specific genes because Herman teaches that they contain methylated CpG neoplastic versus normal tissue.

Conclusion

11. No claims allowable over the art.

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Leng et al. (Biochimica et Biophysica Acta Vol. 174, pages 574-585, 1969) teaches in comparison to native DNA, the melting temperature of methylated DNA is decreased.

B) Yamasaki et al. (Proc. Japan Acad. Vol. 74, Ser. B, pages 210, 1998) teaches methylation of four adenine bases in a decamer DNA duplex decreased the melting temperatures by 9.4 degrees.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of formal matters can be directed to the patent analyst, Pauline Farrier, whose telephone number is (703) 305-3550.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
July 18, 2002

Lisa B. Arthur

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP ~~1800~~ 1600